General

Guideline Title

Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract.

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Jan. 37 p. (Technology appraisal guidance; no. 272).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Vinflunine is not recommended within its marketing authorisation for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy.

People currently receiving vinflunine that is not recommended according to the paragraph above should be able to continue treatment until they and their clinician consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Advanced or metastatic transitional cell carcinoma of the urothelial tract

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Oncology

Urology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract

Target Population

Adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing chemotherapy

Interventions and Practices Considered

Vinflunine

Major Outcomes Considered

- Clinical Effectiveness
  - Overall survival
  - Response rates (complete and partial)
  - Duration of stable disease (SD)
  - Rate of disease control
  - Duration of disease control
  - Progression free survival
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Evidence Review Group (ERG) report for this technology appraisal was prepared by Southampton Health Technology Assessments Centre (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description of Manufacturer's Search Strategy

The search strategies are documented and reproducible and fit for purpose despite a few minor omissions and inconsistencies. The ERG re-ran the searches and no additional data relevant to the submission were identified.

Clinical Effectiveness Searches

The clinical effectiveness search strategies are documented and reproducible and a flow chart of search results is tabulated. The minimum NICE database search criteria have not been precisely met as Embase and Medline® In Process (MEIP) were not mentioned although PubMed was searched, which should have also identified the Medline non-indexed records, obviating the need to search MEIP. Only the Central database in the Cochrane Library is recorded as searched. The ERG ran a search on all Cochrane databases and did not identify any other relevant records. Searches were restricted to the English language. The host stated for the clinical searches in manufacturer's submission (MS) was DIMDI, which the ERG does not have access to. All years are recorded as being searched, however the exact range is not clarified.

A randomised controlled trial (RCT) search filter was not used and thus the search would have retrieved non-RCT evidence and adverse events. It is noted that vinflunine was the search term used in DIMDI, with no mention of the trade name Javlor, nor a search on CAS registry drug number. The ERG ran a search on vinflunine or Javlor on Medline, Embase and PubMed and no additional relevant results were retrieved. The MS states N/A (not applicable) for search of company databases.

There is no record of documentation for ongoing trials databases having been searched. Major oncology meetings are documented as hand searched along with Biosis and CAB Abstracts listed as checked for conference proceeding abstracts. There is no reference in the text to hand-searching bibliographic lists to identify further studies.

Statement of the Inclusion/Exclusion Criteria Used in the Study Selection

The MS clearly states the inclusion and exclusion criteria and these are consistent with the final scope issued by NICE, with one exception. The final scope specifies response rates as an outcome but the MS justifies not including this outcome as there would be "no comparative data for response rate in this end of life population with a heavy tumour burden".

The systematic review reported in the MS was not limited to RCTs. Study quality was not stated as an inclusion or exclusion criterion. The only limits specified for study design were that RCTs, phase II studies, systematic reviews and meta-analyses were included whereas non-inferiority studies were excluded.

Setting was not explicitly stated either in the final scope or the inclusion and exclusion criteria. Patients would be under the care of a multi-disciplinary oncology team receiving chemotherapy and other best supportive end of life care.

The MS presents a flow chart, indicating the number of publications identified and excluded at each stage. Reasons for excluding the papers after detailed review are summarised briefly in the flow chart but the number and identity of papers excluded for each reason are not given in the MS. The flow chart introduces an exclusion criterion that was not listed among the exclusion criteria defined a priori: trials that did not reach primary endpoints were excluded. It is unclear whether this would have resulted in any relevant secondary outcomes being excluded.

The MS does not consider bias or study quality at the stages of study searching, screening and selection. Critical appraisal of the RCT is reported in the MS.

Economic Evaluation

Cost-Effectiveness Searches

The cost-effectiveness search strategies are documented and reproducible but there are some minor discrepancies. The minimum NICE database search criteria have not been precisely met. MS records Medline and Embase which were searched using Ovid (no explanation of the rationale for changing host for the cost-effectiveness searches is given). There are no details given of in-house company databases, or ongoing trials databases, being searched. There is no record of Econlit nor NHS Economic Evaluation database (EED) being searched. The ERG searched both of these databases and no results were returned for Vinflunine/Javlor. The search was widened out to bladder cancer on NHS EED, with no additional references not already in the manufacturer's bibliography being retrieved. MS states that "no restrictions were applied to publication date within searches", however line 4 of the Medline strategy clearly limits the search from 2000 to current. The search strategies are limited by English language in the Embase search. A full economic filter has not been used in either database – however relevant cost indexing terms have been exploded. Health related quality of life and resource utilisation searches have also been undertaken on Medline and Embase.

Studies were included if a) the study referred to vinflunine (VFL), b) the study population related to adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of a prior platinum-containing regimen, and c) the study was an economic evaluation. The search yielded no pertinent studies and the MS concluded that there were no relevant cost-effectiveness studies.

Number of Source Documents

Clinical Effectiveness

- One phase III randomised controlled trial (RCT)
- Two non-RCT, single arm, phase II studies

Cost Effectiveness

- No published studies met the criteria for inclusion.
- The manufacturer presented an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Evidence Review Group (ERG) report for this technology appraisal was prepared by Southampton Health Technology Assessments Centre (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description and Critique of the Approach to Validity Assessment

The manufacturer's submission (MS) provides a quality assessment of the randomised controlled trial (RCT) that follows the NICE criteria, based on Centre for Reviews and Dissemination (CRD) methods, and appears appropriate. Quality assessment of the two non-RCTs is based on an ad

hoc list of five criteria (how patient responses were addressed; occurrence of any unexpected drop outs; appropriateness of the patients studied; selective outcome reporting and intent-to-treat analysis) without reference to any validated assessment instruments for non-randomised studies.

Table 1 of the ERG report shows the assessment of study quality for the RCT by the manufacturer and ERG.

Description and Critique of the Manufacturer's Approach to Trial Statistics

Results of all relevant outcome measures are reported. However, the primary and secondary outcomes appear to be given equal priority in the overall synthesis of clinical effectiveness, with the primary outcome (overall survival) listed after secondary outcomes (response rates, response duration, disease control rate, disease control duration).

Both univariate and multivariate analyses were conducted for the survival outcomes; the latter take into account seven prognostic baseline variables that were specified a priori. A potentially clinically important difference between the study arms was that the best supportive care (BSC) arm had a higher proportion of patients with a better performance status at baseline. This is accounted for as a prognostic factor in the multivariate analyses but not accounted for in univariate analyses that were applied to both primary and secondary outcomes.

Description and Critique of the Manufacturer's Approach to the Evidence Synthesis

The tabulated data generally reflect those reported in the primary publications of the three included trials. Within the MS however there are numerous inconsistencies and errors in the summary of clinical effectiveness data. A meta–analysis is not reported in the MS as only one RCT met the inclusion criteria. No indirect comparison is reported in the MS as no other relevant trials met the inclusion criteria specified in the NICE scope.

Summary Statement of Manufacturer's Approach

The quality of the MS based on CRD criteria for a systematic review as assessed by the ERG is shown in Table 2 of the ERG report (see the "Availability of Companion Documents" field).

The systematic review is of good quality according to CRD criteria and the submitted evidence reflects the decision problem defined in the MS. However, no details are given for any of the processes used in the systematic review; it is not reported whether inclusion/exclusion, data extraction and quality assessment were undertaken by a single reviewer or independently by two reviewers.

See Section 3 of the ERG report for more information on methods for analysing clinical effectiveness.

Economic Evaluation

The cost utility analysis uses a 'partitioned-survival' model to estimate the effect of treatment with vinflunine (VFL) plus BSC compared to BSC in adult patients with transitional cell carcinoma of the urothelial tract (TCCU) who have failed a prior platinum-containing regimen. The results are presented as incremental cost-effectiveness ratios (cost per quality-adjusted life-year (QALY) gained).

Natural History

The model has three mutually exclusive health states (Alive, pre-progression; Alive, post-progression; and Dead). The model calculates the proportion of patients in each treatment cohort that is expected to be in each health state, based on estimates of overall survival (OS) and progression-free survival (PFS). For the BSC cohort, OS and PFS are taken from the RCT for the eligible intention to treat (ITT) population and a Weibull survival model is used to extrapolate beyond the duration of the follow-up in the trial. For the VFL plus BSC cohort, OS and PFS are derived by adjusting the BSC survival using the hazard ratio from the RCT with the proportional hazards assumption. The model uses daily cycles with a time horizon of 5 years.

Sensitivity Analyses

Deterministic sensitivity analyses are presented for most parameters. Additional analyses are presented for alternative analytical scenarios to estimate PFS and OS for VFL plus BSC and BSC. Probabilistic sensitivity analysis was undertaken based on 1000 random iterations.

Model Validation

The model was validated through a series of tests on the model's internal consistency, such as observing whether changes to the model inputs make the expected changes to the model results.

See Section 4 of the ERG report for information on critical appraisal of MS economic evaluation by the ERG.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions on Cost-Effectiveness

Availability and Nature of Evidence

The Committee considered evidence on the cost-effectiveness of vinflunine compared with best supportive care, including quality-of-life estimates, costs and incremental cost-effectiveness ratios (ICERs) presented by the manufacture.

Uncertainties around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee noted that the modelled hazard ratios of overall survival were based on the multivariate analysis of the results for the eligible

intention-to-treat (ITT) population and that these results were more favourable for vinflunine than those obtained from the ITT population. The Committee was aware that the costs for the intravenous administration of vinflunine included in the manufacturer's model were based on out-of-date National Health Service healthcare resource group (NHS HRG) figures which were lower than current estimates.

The Committee considered the manufacturer's lack of inclusion of vial wastage in the model to be inappropriate because of the small number of patients who would be treated with vinflunine at any one centre and time.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values/Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee noted that the pre-progression utility was based on answers to 1 of the 30 questions in the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire, which asked patients to rate their overall quality of life during the past week. The Committee considered that this question may have to be interpreted with caution because a patient's quality of life in the last week of a treatment cycle may not reflect their quality of life for the whole period before disease progression.

It also noted that established algorithms for mapping EORTC responses to EQ-5D exist but were not used by the manufacturer.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost-Effective?

No subgroups were identified in this appraisal.

What Are the Key Drivers of Cost-Effectiveness?

The Committee noted the large incremental costs of £13,100 for 0.131 quality-adjusted life-year (QALY) gain.

The Committee noted that in the manufacturer's sensitivity analyses the inclusion of vial wastage and the use of a lower preprogression utility value increased the incremental cost-effectiveness ratio (ICER) significantly from the base case (to £121,100 and £133,100 per QALY gained respectively). It also noted that in the ERG's exploratory analysis, based on Kaplan–Meier estimates of survival from the ITT population rather than the eligible ITT population, the ICER was £126,400 per QALY gained.

Most Likely Cost-Effectiveness Estimate (Given as an ICER)

The Committee agreed that the most plausible estimate of the ICER for vinflunine plus best supportive care compared with best supportive care alone was above £120,000 per QALY gained.

See Sections 3 and 4 of the original guideline document for details of the economic analysis provided by the manufacturer, the Evidence Review Group comments, and the Appraisal Committee considerations.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD) and were provided with the opportunity to appeal against the final appraisal determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

The Appraisal Committee considered clinical and cost-effectiveness evidence and a review of this submission by the Evidence Review Group. For clinical effectiveness, one randomised controlled trial was the main source of evidence. For cost-effectiveness, the manufacturer's model was considered.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate recommendation for the use of vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract

Potential Harms

According to the summary of product characteristics (SPC), common undesirable effects associated with vinflunine include haematological disorders (neutropenia and anaemia), gastrointestinal disorders (constipation, nausea, stomatitis, vomiting, abdominal pain and diarrhoea), and general disorders (asthenia/fatigue).

For full details of side effects and contraindications, see the summary of product characteristics available at http://emc.medicines.org.uk/.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Clinical Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- The technology in this appraisal may not be the only treatment for advanced or metastatic transitional cell carcinoma of the urothelial tract. Therefore, if a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources when the clinician concludes and the patient agrees that the

recommended technology is the most appropriate to use, based on a discussion of all available treatments.

- NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on the NICE website (http://guidance.nice.org.uk/TA272).
  - A costing statement explaining the resource impact of this guidance

Implementation Tools

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Jan. 37 p. (Technology appraisal guidance; no. 272).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Jan

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Professor Darren Ashcroft, Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester; Dr Matthew Bradley, Value Demonstration Director, AstraZeneca; Dr Brian Buckley, Lay member; Professor Usha Chakravarthy, Professor of Ophthalmology and Vision Sciences, Queen's University of Belfast; Professor Peter Clark (*Chair*) Consultant Medical Oncologist, Clatterbridge Centre for Oncology; Dr Ian Davidson, Lecturer in Rehabilitation, University of Manchester; Dr Martin Duerden, Assistant Medical Director, Betsi Cadwaladr University Health Board; Dr Alexander Dyker, Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle; Gillian Ells, Prescribing Advisor, NHS Sussex Downs and Weald; Dr Jon Fear, Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds; Paula Ghaneh, Senior Lecturer and Honorary Consultant, University of Liverpool; Niru Goenka, Consultant Physician, Countess of Chester NHS Foundation Trust; Dr Susan Griffin, Research Fellow, Centre for Health Economics, University of York; Professor Carol Haigh, Professor in Nursing, Manchester Metropolitan University; Alison Hawdale, Lay member; Professor Peter Jones, Emeritus Professor of Statistics, Keele University; Dr Vincent Kirkbride, Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield; Dr Rachel Lewis, Doctoral Researcher, Manchester Business School; Dr Anne McCune, Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust; Professor Jonathan Michaels (*Vice Chair*), Professor of Vascular Surgery, University of Sheffield; Dr Neil Milner, General Medical Practitioner, Tramways Medical Centre; Professor Femi Oyebode, Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health; Dr John Radford, Director of Public Health, Rotherham Primary Care Trust; Dr Phillip Rutledge, GP and Consultant in Medicines Management, NHS Lothian; Dr Brian Shine, Consultant Chemical Pathologist, John Radcliffe Hospital; Dr Murray D Smith, Associate Professor in Social Research in Medicines and Health, University of Nottingham; Paddy Storrie, Lay member; Dr Cathryn Thomas, GP and Associate Professor, University of Birmingham; Charles Waddicor, Chief Executive, NHS Berkshire; Mike Wallace, Health Economics and Reimbursement Director, Johnson & Johnson Medical Ltd

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Cooper K, Frampton GK, Mendes D, Bryant J. Vinflunine for the second-line treatment of transitional cell carcinoma of the urothelial tract. Evidence review group report. Southampton (UK): Southampton Health Technology Assessments Centre, Wessex Institute, University of Southampton; 2010 Sep 29. 62 p. Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract. Costing statement. London (UK):

National Institute for Health and Clinical Excellence (NICE); 2013 Jan 23. 3 p. (Technology appraisal; no. 272). Electronic copies: Available in PDF from the NICE Web site .

Patient Resources

The following is available:

- Vinflunine for previously treated advanced or metastatic transitional cell cancer of the urothelial tract. Information for the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Jan 23. 5 p. (Technology appraisal; no. 272). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on May 1, 2013.

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